

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- **BLACK BORDERS**
- **TEXT CUT OFF AT TOP, BOTTOM OR SIDES**
- **FADED TEXT**
- **ILLEGIBLE TEXT**
- **SKEWED/SLANTED IMAGES**
- **COLORED PHOTOS**
- **BLACK OR VERY BLACK AND WHITE DARK PHOTOS**
- **GRAY SCALE DOCUMENTS**

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**



⑫ EUROPEAN PATENT APPLICATION

⑬

⑭ Application number: 84305260.6

⑮ Date of filing: 02.08.84

⑯ Int. Cl. 4: A 61 K 37/24, A 61 K 9/20

⑯ Priority: 05.08.83 US 520834
27.07.84 US 635236

⑰ Applicant: Plunkett, Earl Robert, 34 Kingspark Crescent,
London Ontario N6H 4C4 (CA)
Applicant: Wolfe, Bernard Martin Joseph, 17 Metamora
Crescent, London Ontario N6G 1R2 (GB)

⑲ Date of publication of application: 03.04.85
Bulletin 85/14

⑳ Inventor: Plunkett, Earl Robert, 34 Kingspark Crescent,
London Ontario N6H 4C4 (CA)
Inventor: Wolfe, Bernard Martin Joseph, 17 Metamora
Crescent, London Ontario N6G 1R2 (GB)

㉑ Designated Contracting States: AT BE CH DE FR GB IT
L I L U N L S E

㉒ Representative: Lawrence, Peter Robin Broughton et al,
GILL JENNINGS & EVERY 53-54 Chancery Lane, London
WC2A 1HN (GB)

㉓ A method of hormonal treatment of peri-menopausal, menopausal and post-menopausal disorders and multi-preparation
pack therefor.

㉔ Pharmaceutical compositions comprise an estrogen and a
progestogen, generally in the form of a unit dosage containing
both or a pack containing unit dosages of each. The size of each
unit dosage is normally between 0.005 mg and 2.5 mg estrogen
and 0.25 mg and 30 mg progestogen. Slow release compositions
may provide similar dosages. The administration of these low
dosages continuously, or of progestogen continuously and estro-
gen for periods of 20 to 120 days followed by an interval of 3 to 7
days, is useful for treating menopausal (including peri-
menopausal and post-menopausal) disorders in women.

A2

EP 0 136 011

Earl Robert PLUNKETT and
Bernard Martin Joseph WOLFE

A METHOD OF HORMONAL TREATMENT OF PERI-MENOPAUSAL, MENOPAUSAL AND POST-MENOPAUSAL DISORDERS AND MULTI-PREPARED PACK THEREFOR.

This invention relates to products for hormonal treatment for menopausal (including perimenopausal and post-menopausal) disorders in women, and particularly for a treatment involving the continuous administration of a progestogen in conjunction with an estrogen. The invention further relates to 5 a pharmaceutical composition comprising selected dosage units of progestogen and estrogen. In another aspect, the invention is concerned with a regimen comprising the continuous administration of progestogen in conjunction with the cyclical administration of estrogen and to a multi-preparation pack containing selected dosage units of progestogen and estrogen and particularly 10 adapted to such regimen.

Perimenopausal (i.e. over approximately forty years of age), menopausal and post-menopausal women frequently experience a large variety of conditions and disorders which have been attributed to estrogen deprivation due to ovarian failure. The duration of these disorders can be extremely 15 variable, and include hot flushes which can be devastating in some women and very mild in others. Dryness of the vagina associated with susceptibility to minor infections, and frequently associated with discomfort during intercourse, is another symptom which may be directly related to the decrease in estrogen availability.

20 In a long-term sense, one of the most health-threatening aspects of the menopause is the loss of mineral from bone (osteoporosis) which produces a decrease in bone mass and generates a serious risk of fractures. For example, evidence exists that there is a six-fold increase in fractures in 25 post-menopausal women as opposed to men of the same age (Garraway et al, Mayo Clinic Proceedings, 54, 701-707, 1979). These fractures, of course, carry a high complication rate among older people, a marked increase in disability and general morbidity, and certainly an increased risk of mortality.

Another serious health-threatening aspect of the menopause is the impressive loss of protection against heart attacks which is enjoyed by 30 younger women up to the age of 60, when compared to men of the same age. The steep increase in mean serum cholesterol concentration which occurs around the menopause (during the fourth and fifth decades) may contribute importantly to the progressive increase in death from ischemic heart disease in older women. In the eighth and ninth decades, the incidence of deaths from ischemic heart 35 disease approaches that of men (Havlik, R.J. and Manning-Feinleid, P.H. 1979,

NIH Publication No. 79-1610, U.S. Department of HEW).

In addition to the above-mentioned major physical problems, some women experience a larger variety of other symptoms ranging from depression, insomnia, and nervousness, to symptoms of arthritis and so forth.

5 It is generally agreed that estrogen is the most effective agent for the control or prevention of menopausal flushes and vaginal atrophy. It is effective in retarding or preventing the appearance of clinical evidence of osteoporosis. In appropriate doses, when combined with dl-norgestrel (or laevo-norgestrel), a favourable effect upon blood lipids is also seen.

10 Problems with estrogen therapy do exist, however, and have been widely explored and documented in the medical literature. The means by which estrogen has been administered, generally speaking, involves either the use of estrogen alone or estrogen plus a progestogen.

Estrogen alone, given in small doses on a continuous basis, is effective in most patients for the control of the above symptoms and problems associated therewith. However, although the vast majority of women taking continuous low-dose estrogen will not have bleeding for many months or even years, there is a distinct risk posed by this routine of silently (i.e. exhibiting no overt symptoms) developing "hyperplasia of the endometrium".

20 This term refers, of course, to an overstimulation of the lining of the uterus which can become premalignant, coupled with the possibility that the patient will eventually develop cancer of the uterine lining even under such a low-dose regimen (Gusberg et al, *Obstetrics and Gynaecology*, 17, 397-412, 1961).

25 Estrogen alone can also be given in cycles, usually 21-25 days on treatment and 5-7 days off treatment. Again, if small doses of estrogen are required to control the symptoms and it is used in this fashion, only about 10% of women will experience withdrawal bleeding between the cycles of actual treatment. However, one must again be concerned by the risk of developing 30 endometrial hyperplasia and by the increased relative risk of developing cancer of the uterus (Research on the Menopause: Report of a W.H.O. Scientific Group, 53-68, 1981).

The addition of progestogen for the last 7-10 days of each estrogen cycle will virtually eliminate the concern about developing endometrial 35 hyperplasia and probably reduce the risk of developing endometrial carcinoma

below that of the untreated general population. However, withdrawal bleeding will occur regularly in this routine and this is highly unacceptable to most older women (Whitehead, Am. J. Obs/Gyn., 142, 6, 791-795, 1982).

Still another routine for estrogen administration would involve a

5 formulation such as those found in birth control pills which contain relatively small doses of estrogen over the full 20-21 day treatment cycle, plus very substantial doses of potent progestogens over the same period of time. This routine, of course, not only produces withdrawal bleeding on each cycle, but is further unacceptable because such formulations have been shown 10 to carry an increased risk of developing arterial complications such as stroke or myocardial infarction in older women about the age of 35-40. This is especially true if the individual is a smoker of cigarettes (Plunkett, Am. J. Obs/Gyn. 142, 6, 747-751, 1982).

Therapeutic regimens employing a progestogen alone require relatively

15 large doses in order to control hot flushes. Moreover, use of a progestogen alone does not prevent atrophy of the vaginal mucosa, although it may help to prevent osteoporosis. However, a progestogen administered in large doses, together with large amounts of a synthetic estrogen, induces changes in blood 20 lipids which may promote arteriosclerotic changes and have been implicated in the appearance of strokes and myocardial infarction among women taking oral contraceptives in their later reproductive years, (Plunkett, *supra*).

The present invention provides a novel therapeutic method and product involving the use of low dosage levels of estrogens and progestogens, which method is designed to avoid or minimize bleeding and 25 prevent overstimulation of the lining of the uterus while producing favourable changes in blood lipids. In particular, the method involves continuous and uninterrupted administration of very small doses of a progestogen along with administration of an estrogen, the latter being cyclical, where required (for example, with perimenopausal women). The method specifically provides for 30 treatment of menopausal or post-menopausal disorders in a woman comprising either:

A. continuously and uninterruptedly administering a progestogen and an estrogen to said woman, or

B. continuously and uninterruptedly administering a progestogen and 35 cyclically administering an estrogen to said woman by repetitively using a dosage regimen comprising:

(i) administering said estrogen continuously for a period of time between about 20 and about 120 days, followed by

(ii) terminating administering said estrogen for a period of time between about 3 and about 7 days.

5 The term "perimenopausal" refers to women of approximately forty years of age and older, who have not yet definitely arrived at menopause but who are experiencing symptoms associated with menopause.

10 The term "continuous" as applied in the specification and the claims to "administration" means that the frequency of administration is at least once daily. Thus, administration, e.g. every other day or once every third day, is not "continuous" for purposes of this invention. Note, however, that the frequency of administration may be greater than once daily and still be "continuous", e.g. twice or even three times daily so long as the dosage level as specified herein is not exceeded.

15 The term "uninterrupted" means that there is no break in the treatment. Thus "continuous, uninterrupted administration" of a progestogen would mean that the progestogen is administered at least once daily essentially in perpetuity or until the entire treatment is ended. In this regard, it should be noted that "cyclical" administration means that there is 20 a break in administration and that, therefore, by definition, cyclical administration cannot be "uninterrupted".

25 The term "dosage level" means the total amount of estrogen or progestogen administered per day. Thus, for example, the "continuous administration" of a progestogen to a woman at a "dosage level" of 75 micrograms means that the woman receives a total of 75 micrograms of progestogen on a daily basis, whether the progestogen is administered as a single 75 microgram dose or, e.g. three separate 25 microgram doses. It is noted that the most conventional means of continuously administering an estrogen or progestogen is as a single daily oral dose at the prescribed 30 dosage level. Parenteral modes of administration, which provide a slow release of the progestogen, could be substituted for the oral route.

35 Thus, the invention realizes the objects of providing a therapeutic method allowing for the administration of an estrogen, controlling hot flushes, restoring the vaginal mucosa to a healthier state, preventing the development of the dimineralization of bones as well as preventing changes in

lipids which predispose to cardiovascular disease, over long periods of treatment, which method does not, however, initiate bleeding or increase the risk of endometrial carcinoma.

In another aspect, the invention provides a pharmaceutical composition for hormonal treatment of menopausal or post-menopausal disorders in a woman, which comprises a dosage unit of a progestogen and a dosage unit of an estrogen for continuous administration wherein the units comprise a progestogen in the range of 0.025 to 30 mg and an estrogen in the range of 0.005 to 2.5 mg together with a pharmaceutically acceptable inert carrier.

10 The actual unit dosages are selected according to conventionally known methods, e.g. body weight of patient and biological activity of the hormones, with the ultimate goal of producing the desired result with the minimum quantities of hormones.

The interruption of the estrogen administration is required in 15 perimenopausal women to maintain normal periods and may be required in certain jurisdictions due to health concerns - particularly overstimulation of the lining of the uterus to cause a pre-malignant condition. The absence of estrogen for a short period allows the lining of the uterus to be sloughed and any pre-malignancy thus avoided. However, the inventors believe that even 20 with continuous administration of estrogen, the presence of progestogen will give rise to sufficient atrification of the uterus that no such condition would be likely to occur.

A further and important object of the invention is to provide the means whereby a woman may receive the proper quantities and dosage units of 25 the progestogen and estrogen for adherence to the prescribed regimen wherein the dosage of estrogen is cyclically administered. Such means takes the form of a multi-preparation pack, which facilitates administration by a nurse or physician in appropriate circumstances or, more usually, self-administration by the woman.

30 The multi-preparation pack contains sufficient dosage units of progestogen and estrogen for continuous administration of both said progestogen and said estrogen for a period of from about 20 to 120 days optionally plus an additional number of dosage units of progestogen for administration for an additional period of time of from about 3 to about 7 35 days during which administration of said estrogen is terminated. Preferably the estrogen is administered for a period in the range 30 to 120 days.

A preferred product comprises one or more unit dosages of a composition containing an estrogen and a progestogen with a suitable pharmaceutically inert carrier in which the unit dosages each contain less than 2.5 mg of estrogen and less than 30 mg of progestogen. Preferably the product is in the form of a multi-preparation pack comprising a plurality of these unit dosages.

The product may alternatively be in the form of a parenteral slow release composition comprising an estrogen and a progestogen, usually in the form of an implant or an intramuscular depot, which releases dosages equivalent to orally administered daily dosages of 0.005 to 2.5 mg of estrogen and 0.025 to 30 mg progestogen.

Some type of product for use in the treatment of menopausal disorders by the continuous and uninterrupted administration of a progestogen in conjunction with the administration of an estrogen comprises unit dosages of less than 2.5 mg estrogen and unit dosages of less than 30 mg of progestogen, preferably together in a single container. Usually this type of product comprises a multi-preparation pack comprising unit dosages of estrogen sufficient for a period of treatment of 20 to 120 days, preferably 20 to 120 days, and unit dosages of progestogen sufficient for at least the same period of treatment and preferably for an additional period of treatment of 3 to 7 days. The product is formulated to permit administration separately or simultaneously of the unit dosages of estrogen and progestogen. The dosages 25 may contain one only or both of estrogen and progestogen. During periods of treatment when both hormones are to be administered the dosages of estrogen and progestogen may be taken simultaneously or separately, but are preferably taken simultaneously and usually both hormones will be contained in the same unit dosage in the 30 form of, for example, a pill, capsule or tablet.

The estrogens used in the present disclosure may be those which are orally active and are suitable for oral contraception and selected from natural estrogens such as estradiol, estradiol-17-beta, estradiol valerate, conjugated equine estrogens, piperazine estrone sulphate, estrone, estriol, estriol succinate and

polyestriol phosphate, or from synthetic estrogens such as ethinyl estradiol, quinestranol and mestranol. The natural estrogens are preferred.

The progestogen is again selected from those which are orally active and suitable for oral contraceptives and may be, for example, dl-norgestrel, laevo-norgestrel, norethindrone (norethisterone), norethindrone acetate, ethynodiol diacetate, medroxyprogesterone acetate, cyproterone acetate norethynodrel, hydrogesterone, allylestrenol, quingestanol acetate, lynoestrenol, medrogestone, norgestriene, dimethisterone and ethisterone.

In the following Tables 1A and 1B are listed preferred unit dosages, minimum unit dosages and maximum unit dosages for the estrogens and progestogens useful in this invention. The quantities are determined by the biological activities of the particular substances as obtained commercially from sources that normally supply them in micronised form.

TABLE 1A
ESTROGENS

		<u>Preferred</u>	<u>Dosage</u>	(mg/day)
			<u>Minimum</u>	<u>Maximum</u>
5 Natural estrogens (steroids)				
	Estradiol	1	0.500	2
	Estradiol-17 β	1	0.500	2
	Estradiol valerate	1	0.500	2
	Conjugated equine estrogens	0.600	0.300	2.5
10	Estrone	0.600	0.300	2.5
	Piperazine estrone sulphate (estropipate)	0.500	0.250	2.5
	Estriol*	0.100	0.050	0.500
	Estriol succinate*	0.100	0.050	0.500
15	Polyestriol phosphate*	0.100	0.050	0.500
Synthetic estrogens (steroids)				
	Ethinyl estradiol	0.010	0.005	0.020
	Mestranol	0.015	0.005	0.040
	Quinestranol	0.010	0.005	0.030
20	It may be noted that of the estrogens of Table 1A, the estriol preparations marked with an asterisk (*) have lower preference than estradiols or estrones because they fail to spare bone in post-menopausal women.			
	However, they could be combined with natural or synthetic estrogens for the purpose of the invention. Also, it is preferable that the following			
25	non-steroidal estrogens - although useful in this invention - be avoided for women who have not definitely arrived at menopause (who could become pregnant) - estrogens of this type being known to induce vaginal cancer and other abnormalities in offspring if taken during the pregnancy:			
	Stilboestrol	0.100	0.020	2
30	Stilboestrol dipropionate	0.100	0.020	2
	Diethylstilboestrol	1	0.400	2.5
	Chlorotrianisene	2	1	2.5
	Benzoestrol	2	0.5	2.5
	Dienoestrol	0.500	0.200	2.5
35	Hexoestrol	0.500	0.200	2.5
	Methallenoestril	1	0.500	2.5

TABLE 1B
PROGESTOGENS

		<u>Preferred</u>	<u>Dosage</u>	(mg/day)
			<u>Minimum</u>	<u>Maximum</u>
5	Laevo-norgestrel	0.050	0.025	0.075
	dl-norgestrel	0.100	0.050	0.150
	Norethindrone (norethisterone)	0.30	0.15	1.0
	Norethindrone (norethisterone) acetate	0.20	0.10	1.0
10	Ethynodiol diacetate	0.30	0.10	1.0
	Dydrogesterone	10	5	30
	Medroxyprogesterone acetate	2.5	1	15
	Norethynodrel	1	0.200	5
	Allylestrenol	2	1	10
15	Lynoestrenol	0.200	0.100	2
	Quingestanol acetate	0.200	0.050	1
	Medrogestone	2	1	10
	Norgestrienone	0.050	0.020	0.200
	Dimethisterone	1	0.500	15
20	Ethisterone	2.5	1	25
	Cyproterone acetate	0.500	0.100	10
	Chlormadinone acetate	0.300	0.100	1
	Megestrol acetate	1	0.100	10

Although chlormadinone acetate and megestrol are useful in the context of this invention, it has been speculated that these progestogens may pre-dispose breast tumors, although no clinical proof exists to that effect. However, unless and until such suspicions are proven to be without foundation, 5 these compounds are clearly of lower preference.

The estrogen/progestogen combinations may be administered non-orally by implants or intramuscular injections. Generally speaking, the required dosages are based upon somewhat lower daily dosage levels than those required for the orally administered estrogens and progestogens, for the simple reason 10 that the former are directly released into the bloodstream with consequently greater activity than the same compounds when orally ingested.

Estradiol, estradiol valerate and estradiol 17- β are suitable candidates for estrogen implants, in maximum and minimum amounts of 100 mg and 20 mg, with 100 mg preferred. These quantities will be suitable for 15 slow-release implants intended for replacement every 3 to 12 months.

Suitable progestogen implants and intramuscular injections are set forth in Table 1C.

TABLE 1C

Total Quantity (mg)

		<u>Period</u>	<u>Preferred</u>	<u>Minimum</u>	<u>Maximum</u>
<u>Progestogen implants</u>					
5	Laevonorgestrel	every 2-5 yr.	50	25	100
	dl-norgestrel	every 2-5 yr.	100	50	200
	Norgestrienone	every 1-2 yr.	100	25	200
	Norethindrone				
	acetate	every 2-4 mon.	100	25	200
10	<u>Intramuscular progestogen depots</u>				
	Medroxyprogesterone				
	acetate	every 3 mon.	150	50	500
	Norethindrone				
	enanthate	every 3 mon.	50	20	400
15	Gestronol				
	hexanoate	every 3 mon.	100	50	400
	Algestone acetophenide	monthly	50	20	300
	Hydroxyprogesterone				
	hexanoate	weekly	100	50	250
20	Hydroxyprogesterone				
	caproate	bi-weekly	100	50	250

5 *d*1-Norgestrel, laevo norgestrel (the common name for *d*-13 β -ethyl-17 α -ethinyl-17 β -hydroxy-4-en-3-one), norethindrone (common name for 17-hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one), ethynodiol diacetate (common name for 19-nor-17 α -pregn-4-en-20-yne-3 β , 17-diol diacetate), norethindrone acetate, and cyproterone acetate may also be administered by injection. It will be readily appreciated by those skilled in the art that any other synthetic progestogen which is orally active or effective for use in conjunction with contraception is also suitable for use in this invention.

10 Any of the suitable estrogens and progestogens (particularly those listed in the foregoing tables) may be combined with one another in the quantities recited to give estrogen/progestogen combinations within the purview of the invention. Especially preferred combinations are those containing the estradiols or conjugated equine estrogens and the norgestrels norethindrones, or medroxyprogesterones. Thus, especially preferred 15 combinations are:

Table 1D

	Estradiol/Laevo-norgestrel
	Estradiol 17 β /Laevo-norgestrel
	Estradiol valerate/Laevo-norgestrel
	Conjugated equine estrogens/Laevo-norgestrel
20	Estradiol/dl-norgestrel
	Estradiol 17 β /dl-norgestrel
	Estradiol valerate/dl-norgestrel
	Conjugatged equine estrogens/dl-norgestrel
	Estradiol/Norethindrone (norethisteron)
25	Estradiol 17 β /Norethindrone (norethisterone)
	Estradiol valerate/Norethindrone (norethisterone)
	Conjugated equine estrogens/Norethindrone (norethisterone)
	Estradiol/Norethindrone (norethisterone) acetate
	Estradiol 17 β /Norethindrone (norethisterone) acetate
30	Estradiol valerate/Norethindrone (norethisterone) acetate
	Conjugated equine estrogen/Norethindrone (norethisterone) acetate
	Estradiol/Medroxyprogesterone acetate
	Estradiol 17 β /Medroxyprogesterone acetate
	Estradiol valerate/Medroxyprogesterone acetate
35	Conjugated equine estrogen/Medroxyprogesterone acetate

The maximum, minimum and preferred dosage levels for the respective estrogens and progestogens in the foregoing combinations are as recited in the tables.

5 The composition of the invention is usually administered orally in admixture with a pharmaceutically acceptable inert carrier. The estrogen and progestogen can be compounded in any pharmaceutically acceptable inert (non-toxic) form. The packaging can be any system convenient for proper delivery. With the preferred orally administrable form, the pharmaceutical carrier can be any of the conventionally employed carriers, for example 10 pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and similar substances. The compositions may be formulated into solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations, etc.

15 One of the unique aspects of this invention is the adaptation of the multi-preparation pack to the continuous uninterrupted administration of a progestogen and an estrogen when estrogen is administered in a cyclic fashion. The duration of the estrogen cycle can be very variable, with continuous administration ranging between 20 and 120 days followed by a break 20 (i.e. interruption) in estrogen administration ranging anywhere from about 3 to about 7 days. However, if the estrogen is discontinued for a period longer than 5 days, recurrence of hot flushes is most likely to occur in a number of patients.

25 The multi-pack dispensing system may be accommodated by conventional packaging equipment, e.g. transparent strip foil packages continuously arranged in daily dosages or other conventional means in the art. Where the multi-pack is employed for the cyclical administration of an estrogen in combination with a progestogen, the pack would conveniently comprise a transparent strip foil package with the combined unit daily dosages arranged 30 continuously with, for example, up to a total of 120 such dosages, the 3 to 7 unit dosages of progestogen being located at the end of the combined daily unit dosages whereby they would be taken at the end of the series.

35 The inventors have developed clinical evidence from this routine that the amounts of estrogen and progestogen required to control flushes, vaginal symptoms and associated subjective symptoms are very small. Preliminary

metabolic responses of the subjects indicate favourable changes toward the lower blood lipid levels found in younger premenopausal women.

EXAMPLE 1

An experimental study of thirty women was instituted under a 5 randomized double blind protocol with crossover and involved the administration of placebos, progestogen only, estrogen only and the combination of the continuous, uninterrupted progestogen/cyclic estrogen treatment. Treatment comprised administering each hormone and the combination as follows: (1) estrogen alone for two months; (2) progestogen alone for two 10 months; (3) combination therapy using (1) and (2) for six months. Each period of administering a hormone or the combination was followed by a one month period of placebo (substance with no endocrine activity) administration. The estrogen was micronized 17β -estradiol administered at a daily dosage level of 1 milligram, while the progestogen was dl-norgestrel 15 administered at a dosage level of 75 micrograms.

Of 30 women who have completed this study, 22, on the basis of their responses throughout the fourteen months of observation, selected the combination treatment and requested to continue it. This represents a high level of acceptability.

20

EXAMPLE 2

In a follow-up phase of observation, 17 subjects (with intact uterus) have completed a total of 125 lunar months of the combination therapy (continuous, uninterrupted administration of dl-norgestrel, cyclic administration of 17β -estradiol). None of the patients experienced 25 "bleeding" which required protection. 1.6 percent of the cycles involved spotting requiring no protection. 98.4 percent of the cycles were completely clear.

The combination therapy has been associated with no evidence whatsoever of endometrial hyperplasia (overstimulation of the lining of the 30 uterus). One patient, after the 2-month phase of taking estrogen only (in the double blind study) did show evidence not only of hyperplasia of the endometrium but also had atypical findings which could be interpreted as indicative of a premalignant change. Addition of the small (75 microgram) dosage level of progestogen (dl-norgestrel) for two weeks only followed by 35 full dilatation and curettage revealed that the endometrium had become

completely atrophic once again and a total reversal of the previous findings were noted.

As an alternative to dl-norgestrol, laevo-norgestral may be used. Since the dl-norgestrol consists of equal parts of the dextro (inactive) and 5 laevo (active) forms, only half the quantity of laevo-norgestrol is used with the same effect. Thus, if laevo-norgestrol is substituted for dl-norgestrol in the foregoing examples, the laevo-norgestrol dosage level is 37.5 micrograms.

At least five cases of young women who required removal of ovaries 10 and uterus because of severe endometriosis have also been successfully treated by the above combination. These women rarely have total removal of the endometriotic tissue. It is important to treat these patients with estrogen replacement therapy to prevent the early appearance of bone demineralization (osteoporosis), elevation of cholesterol and triglycerides and to control 15 severe hot flushes and vaginal atrophy. If patients such as these are treated with estrogen alone, they frequently develop recurrence of pain symptoms due to residual endometriosis being restimulated by the administered estrogen. Because the inventors' combination therapy tends to promote atrophy of the 20 lining of the uterus (endometrium) no matter whether it is located normally within the uterus or in the endometriotic tissue in the pelvis, it is found that these patients tolerate the treatment very well and do not have a recurrence or reactivation of their endometriosis. Furthermore, even small doses of estrogen in combination with the continuous progestogen routine is sufficient to control the severe hot flushes which such patients experience.

25 Thus this invention permits control of menopausal disorders including hot flushes and vaginal atrophy along with many of the subjective symptoms. Further, given that both components of the combination therapy are considered to be effective in retarding osteoporosis, long term therapy to prevent this disabling disease should be effective.

30 Additionally, the risk of developing endometrial (uterine) cancer from the combination therapy should, at a minimum, be reduced to the normal incidence of the general population as opposed to the increased risk which has in fact been demonstrated to occur using estrogen-only treatment. The inventors have in fact developed some evidence suggestive that the combination therapy reduces the risk of premalignant endometrial changes, which may reduce 35

the risk of developing endometrial cancer. The reduction in bleeding or spotting in patients taking the combination therapy makes it much more desirable relative to known treatments, particularly to older women.

The following describes directions which may be applied to a 5 multi-preparation pack specifically adapted to the cyclical administration of estrogen together with the continuous administration of progestogen in accordance with one embodiment of the invention:

10 ABOUT THESE TABLETS

(The tablet set herein) is used to control menopausal symptoms. It is not a birth control pill and cannot be relied upon to prevent pregnancy.

15 Oral contraceptives should not be taken at the same time as these tablets and, if necessary, you should therefore ask your doctor about alternative means of mechanical protection.

20 When treatment is first started, tingling of the breasts slight nausea or occasional vaginal bleeding may occur - this should settle after a short time.

25 If you have any unusual symptoms, contact your doctor.

To be taken under medical supervision.

30 HOW TO USE THIS PACK

Whether you are menstruating regularly or not, take the first tablet on a day suitable to yourself until all the tablets have been consumed.

35 THE LAST SEVEN TABLETS OF THE DIFFERENT COLOUR ARE TO BE TAKEN ONLY WHEN ALL OTHERS HAVE BEEN CONSUMED.

Alternatively, the foregoing instructions may be printed as a leaflet, and the package instructions modified as follows:

5

Before commencing treatment please read the enclosed instruction leaflet carefully. If you have any difficulties following the instructions please ask your doctor for assistance.

DIRECTIONS

10

To remove a tablet, press firmly with your thumb on the appropriate clear plastic bubble. This may be helped by holding the card so that your other fingers surround the aluminum foil through which the tablet will emerge.

15

A multi-preparation pack suitable for administration of tablets in accordance with the regimen described above is illustrated in the single figure of the drawings. A bubble pack 10 (which may be folded along the line 20 10a) is sold in a protective sleeve 11, upon the rear of which are printed the directions for use and salient facts concerning the tablets, as indicated at 12 in the drawing. When removed from the protective sleeve by the consumer, the bubble pack contains as many tablets as the number of days which the pack is intended to cover (in this example, one hundred and twenty days). 25 Optionally, the individual bubble segments may be numbered from one to one hundred and twenty but it is important that the last few segments, which contain the progestogen-only tablets, be clearly distinguished from the remainder of these segments. In the present example, the segments 13 containing the first one hundred and thirteen tablets (combination 30 progestogen/estrogen) are a light colour (for example, white) whilst the last seven segments 14, containing the progestogen-only tablets are a dark colour (red, for example). By following the directions on the sleeve and observing the colours on the bubble pack (and the "day numbers", if present) the

0136011

18

consumer will take the combination tablets for the first one hundred and thirteen days and the progestogen tablets for the last seven days. Thereafter, a new package would be opened, whereby the cycle is repeated.

CLAIMS

1. A product that comprises one or more unit dosages of a composition containing an estrogen and a progestogen with a suitable pharmaceutically inert carrier, characterised in that the unit dosages each contain less than 2.5 mg estrogen and less than 30 mg progestogen.
- 5 2. A product according to claim 1 in the form of a multi-preparation pack comprising a plurality of the said unit dosages.
- 10 3. A product in the form of a parenteral slow release composition comprising an estrogen and a progestogen, preferably in the form of an implant or an intramuscular depot, characterised in that the composition releases dosages equivalent to orally administered daily dosages of 0.005 to 2.5 mg estrogen and 0.025 to 30 mg progestogen.
- 15 4. A product for use in the treatment of peri-menopausal, menopausal or post-menopausal disorders by the continuous and uninterrupted administration of a progestogen in conjunction with the administration of an estrogen comprising unit dosages of estrogen and unit dosages of progestogen, preferably together in a single container, characterised in that a unit dosage of estrogen contains less than 2.5 mg estrogen and a unit dosage of progestogen contains less than 30 mg progestogen.
- 20 5. A product according to claim 4 which comprises a multi-preparation pack comprising unit dosages of estrogen sufficient for a period of treatment of 20 to 120 days, preferably 30 to 120 days, and separate unit dosages of progestogen sufficient for at least the same period of treatment and preferably for an additional period of treatment of 3 to 7 days.
- 25 30

6. A product according to any one of claims 1 to 5 in which the estrogen is selected from the following group with the maximum dosages indicated (in mg):

	Estradiol	2
	Estradiol-17 beta	2
5	Estradiol valerate	2.5
	Conjugated equine estrogens	2.5
	Estrone	2.5
	Piperazine estrone sulphate (estropipate)	0.020
10	Ethinyl estradiol	0.040
	Mestranol	0.030

Quinestranol
and the progestogen is selected from the following group with the maximum dosages indicated (in mg):

	Laevo-norgestrel	0.075
15	dl-norgestrel	0.150
	Norethindrone (norethisterone)	1.0
	Norethindrone (norethisterone) acetate	1.0
	Ethynodiol diacetate	1.0
	Dydrogesterone	30
20	Medroxyprogesterone acetate	15
	Norethynodrel	5
	Allylestrenol	10
	Lynoestrenol	2
	Quingestanol acetate	1
25	Medrogestone	10
	Norgestrienone	0.200
	Dimethisterone	15
	Ethisterone	25
	Cyproterone acetate	10.

30 7. A product according to any one of claims 1 to 6 in which the dosages are daily dosages and the estrogen is selected from Table 1A at the dosages indicated therein and the progestogen is selected from Table 1B at the dosages indicated therein.

8. A product according to any one of claims 1 to 7 in which the estrogen and the progestogen are selected from the combinations quoted in Table 1D.
9. A product according to claim 8 in which the estrogen is 17-beta-estradiol and the progestogen is dl- or 5 laevo-norgestrel.
10. A product according to claim 7 in which the estrogen is 17-beta-estradiol at a dosage between 0.5 and 2.0 mg and the progestogen is dl-norgestrel at a dosage between 50 and 150 micrograms, preferably about 75 micrograms.
11. A product according to claim 3 in which the estrogen is selected from estradiol, estradiol valerate and estradiol-17-beta at a maximum total quantity of 100 milligrams and the progestogen is selected from Table 1C 10 at the periods indicated therein and at the quantities between the minimum and maximum indicated therein.
12. A method of treatment of peri-menopausal, menopausal or post-menopausal disorders in a woman comprising administering to the woman a progestogen in conjunction 15 with an estrogen, characterised in that the progestogen is administered continuously and uninterruptedly at a daily dosage of 0.025 to 30 mg and the estrogen is administered at a daily dosage of 0.005 to 2.5 mg.
13. A method according to claim 11 in which the estrogen is administered continuously for a period of 20 to 120 20 days, preferably 30 to 120 days, and then is omitted from being administered for a period of 3 to 7 days.
14. A product for use in the treatment of peri-menopausal, menopausal or post-menopausal disorders by the continuous and uninterrupted administration of a 25 progestogen in conjunction with the administration of an estrogen comprising an estrogen and a progestogen, characterised in that the product is formulated to permit administration, separately or simultaneously, of unit 30 administration.

0136011

22

dosages of the estrogen in amounts up to 2.5 mg and of the progestogen in amounts up to 30 mg.

15. A progestogen for use at a daily dosage of 0.025 to 30 mg in combination with an estrogen for the treatment of peri-menopausal, menopausal or post-menopausal disorders.

10

15

20

25

30

35

0136011

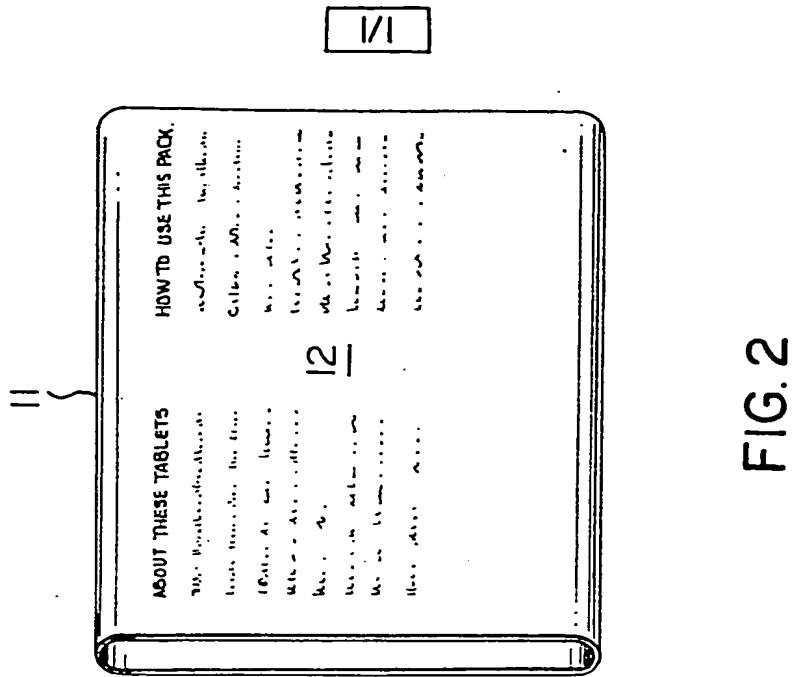


FIG. 2

